REMARKS

Prior to the present amendment, claims 32-36 and 39-43 were under consideration and claims 1 through 31, 37, 38, and 44-46 were canceled. By this amendment, applicants added new claims 47-56. Accordingly, claims 32-36, 39-43, 47-56 are currently under examination. The claim amendments do not add new matter.

Rejection of claims 32-36, 39-42, and 46 under 35U.S.C. § 103(a) over Tormo, et al., and Freyre, et al., as evidenced by Ayala, et al., and Holliger, et al.

In an Advisory Action mailed May 20, 2008, the examiner entered the amendments of May 5, 2008, which was filed in response to a final office action dated January 4, 2008. However, the examiner states that the application is not in condition for allowance. The examiner maintains the rejection of claims 32-36 and 39-42 under the 35 U.S.C. § 103(a) over Tormo, et al. (*APMIS*, 97(12): 1073-80 (1989)), in view of Freyre, et al. (*J. Biotechnol.* 76:157-163 (2000)), as evidenced by Ayala, et al. (*Conf. on Plant-Made Pharmaceuticals 2005*; Abstract), in further view of Holliger, et al. (*PNAS*, 90: 6444-6448 (1993)).

According to the examiner, Tormo discloses the CB/ior-CEA.1 hybridoma which produces a murine monoclonal antibody specific for human carcinoembryonic antigen (CEA). See page 9 of the January 4, 2008 office action. The examiner states that the VH and VL domains of the scFv of the claimed sequences SEQ ID NO: 16 and 17 were derived from the antibody produced by the hybridoma of Tormo.

On page 10 of the January 4, 2008 office action, the examiner acknowledges that Tormo does not disclose scFvs using the VH and VL domains from the parent antibody. The examiner cites Freyre to rectify this deficiency. The examiner asserts that Freyre discloses an scFv produced by using the VH and VL domains of CB/ior-CEA.1, however, it contained mutations, as evidenced by Ayala. The examiner further notes that Ayala (2005) discloses another scFv that was constructed from amplified CB/ior-CEA.1 VH and VL genes, "taking care to avoid the potential introduction of PCR mutations."

"To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art." *MPEP § 2143.03.* "All words in a claim must be considered in judging the patentability of that claim against the prior art." *Id.*

Here, the claimed invention requires an amino acid sequence as set forth in SEQ ID NO: 16/17. The cited references are devoid of any showing of a structural similarity with the claimed invention. None of the cited art references, individually or in combination, disclose or suggest any sequences for a CB/ior-CEA.1 scFv antibody fragment or the sequences of SEQ ID NOs: 16/17. Therefore, the claimed invention is not obvious over the cited art references where all of the claim limitations are not taught or suggested by the prior art.

The lack of any disclosure or suggestion of a sequence for a CB/ior-CEA.1 scFv antibody fragment in the cited art also evidences a lack of reasonable expectation of success. "To reach a proper determination under 35 U.S.C. 103, the examiner must step backward in time and into the shoes worn by the hypothetical 'person of ordinary skill in the art' when the invention was

unknown and just before it was made... impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the facts gleaned from the prior art." *MPEP § 2142.* At least some degree of predictability is required for a showing of obviousness. *MPEP §2143.02.* "Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness." *Id.*

Here, the examiner alleges that there was a reasonable expectation of success in producing the claimed antibody fragments based on the cited prior art because:

> all the materials and reagents were available for producing the recombinant CEA Abs, and ...the importance of VH and VL sequence fidelity in generating a scFv with high affinity binding was established...and Hollinger [*sic.*] provided an alternative method to for [*sic.*] cloning VH and VL domains from a parent Mab into a scFv or diabody structure...

See page 11 of the January 4, 2008 office action.

Applicants respectfully disagree. At the time of the invention in 2002,[1] merely having "all the materials and reagents...available for producing the recombinant CEA Abs" was not sufficient for a reasonable expectation of success for the claimed scFv fragments. At the time of invention, one skilled in the art knew how to produce an scFv antibody fragment derived from the CB/ior-CEA.1 antibody. See, for example, Freyre (2000) at page 158 ("starting with RNA from ior-cea.1 hybridoma cells, we have developed several scFv gene constructions that have been expressed as biologically active antibody fragments..."); and the specification at page 2, lines 29-31, citing Ayala, *Biotechniques*, 13: 790-799 (1992), for disclosing the development of an scFv antibody fragment obtained by PCR of the RNA extracted from the hybridoma for CB/ior-CEA.1.

[1] This application asserts priority to Cuban application number CU 2002/0086 filed on April 29, 2002.

However, scFv antibody fragments developed by previous investigators (*e.g.*, by Freyre, 2000, and Ayala, 1992) failed to exhibit a high affinity for the target antigen CEA and a proper biodistribution in test animals. See the specification at page 2, lines 29-40; see also Ayala (2005), first paragraph, which states that the affinity of the scFv disclosed in Freyre "was shown to be 200 times lower than that of the Fab obtained by enzyme digestion of the original Mab (Perez L et al., 1996)."). Accordingly, merely having "all the materials and reagents" available for producing the recombinant CEA Abs is not sufficient for a reasonable expectation of success for arriving at the claimed scFv fragments.

In determining whether a reasonable expectation of success is present, the examiner further asserts that "the importance of VH and VL sequence fidelity in generating a scFv with high affinity binding was established." See page 11 of the January 4, 2008 office action. To support her assertion, the examiner relies on the hypothesis disclosed in Ayala (2005) that the reduced binding affinity observed by Freyre (2000) may be due to mutations. See the first full paragraph on page 10 of the January 4, 2008 office action. Ayala (2005) states, "A new scFv was constructed from newly amplified CB/ior-CEA.1 VH and VL genes, taking care to avoid the potential introduction of PCR mutations."

Contrary to the examiner's assertion, however, "the importance of VH and VL sequence fidelity in generating a scFv with high affinity binding" was **not** established at the time of the invention in 2002. At the time of the invention, there was nothing predictable about how or what to modify from the CB/ior-CEA.1 hybridoma of Tormo or the the scFv antibody fragments of Freyre in order to arrive at the claimed scFv antibody fragments. The prior art at the time of the

invention did not disclose or predict any sequences for a CB/ior-CEA.1 scFv antibody fragment, any alleged mutations, or any modifications to correct any alleged mutations. None of the cited references disclose any sequences for an scFv antibody fragment. Applicants note that the examiner did not reject original claims 2 and 4 in view of the same combination of cited references. Claims 2 and 4 were directed to scFv sequences comprising SEQ ID NO: 16/17. See the June 7, 2007 office action. In addition, none of the cited references disclose any sequences for a VH or VL domain of the CB/ior-CEA.1 antibody.

The examiner, therefore, exercised impermissible hindsight, especially by relying on Ayala (2005) for allegedly disclosing "the importance of VH and VL sequence fidelity in generating a scFv with high affinity binding." Ayala was published nearly three years after the date on which the present application asserts priority.

Accordingly, there was no reasonable expectation of success for arriving at the claimed scFv antibody fragments. Applicants respectfully request that the examiner reconsiders and withdraws the rejection under 35 U.S.C. §103(a).

Even if the examiner establishes a *prima facie* case of obviousness, which applicants asserts she has not, the specification provides evidence of unexpected results over the prior art. Evidence of unobvious or unexpected advantageous properties, such as superiority in a property the claimed compound shares with the prior art, can rebut *prima facie* obviousness. *MPEP§ 716.02(a)(II)*. Evidence of unexpected properties may be in the form of a direct or indirect comparison of the claimed invention with the closest prior art which is commensurate in scope

with the claims. *MPEP § 716.02(b)(III)*. Applicants may compare the claimed invention with prior art that is more closely related to the invention than the prior art relied upon by the examiner. *MPEP 716.02(e)(I)*.

Here, the claimed invention relates to scFv antibody fragments that were derived from RNA from the parent Mab CB/ior-CEA.1 disclosed in Tormo. See page 3, lines 4-6 of the specification. Tormo does not disclose scFv antibody fragments, as acknowledged by the examiner. See page 10, lines 1-3 of the January 4, 2008 office action. Freyre discloses an scFv antibody fragment that was derived from RNA from the parent Mab CB/ior-CEA.1 disclosed in Tormo. See pages 157- 158 of Freyre. Accordingly, the prior art that is more closely related to the invention than the primary prior art reference relied upon by the examiner (*i.e.*, Tormo) is the Freyre reference.

Throughout the examples in the specification, the inventors provide data comparing various properties of the claimed scFv fragments against an scFv termed "F3." The F3 scFv was previously produced by Ayala (1992) and Perez, et al. *Applied Biochem. Biotechnol.* 24: 79-82, 1996. See, for example, page 21, line 37, to page 22, line 5 of the specification. The gene construct that expresses the F3 scFv antibody fragment disclosed in Ayala (1992) and Perez is the "same" as that disclosed in Freyre. See pages 157-158 of Freyre and page 2, lines 29-40, of the specification. Accordingly, the inventors compared the claimed scFv antibody fragments against an scFv that is analogous to that disclosed in Freyre (2000).

In example 8 of the specification, the claimed scFv is shown to have an affinity constant for the CEA antigen that unexpectedly exhibits "a magnitude more than one order and a half higher than that obtained for F3." See page 24, lines 13-24 of the specification. The inventors further note that Freyre discloses an scFv with no improvements in affinity for human CEA over the scFv previously reported by Ayala (1992). See page 2, lines 29-40, of the specification. See, also, for example, page 3, lines 29-41, of the specification, which states that the claimed scFvs "surprisingly" have a behavior that is "very similar" to the parent Mab CB/ior-CEA.1 and is "very much superior to that of the previously reported scFv."

In example 9 of the specification, the inventors observed that the claimed scFv exhibited comparable *in vivo* detection levels for the target antigen CEA on tumor cells, whereas the scFv termed "F3" exhibited "very low" detection levels. See page 25, line 35 to page 26, line 5 of the specification.

Accordingly, when compared with the closest prior art that discloses a scFv antibody fragment derived from RNA of the Mab CB/ior-CEA.1, the claimed invention exhibits the unexpected properties of, *inter alia*, high affinity for the target antigen CEA and high levels of specific recognition of tumors that produce human CEA. The inventors have presented evidence of unobvious or unexpected advantageous properties over the prior art to rebut *prima facie* obviousness. Applicants respectfully request that the examiner reconsiders and withdraws the rejection under 35 U.S.C. §103(a).

Conclusion

In view of the foregoing amendments and remarks, entry of the amendments to the claims and favorable thereof are respectfully requested. If any additional fees are due or any overpayment has been made in connection with filing this paper, please charge or credit our Deposit Account No. 08-2461 for such sum. If the examiner has any questions or concerns regarding this amendment, she is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,

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